



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

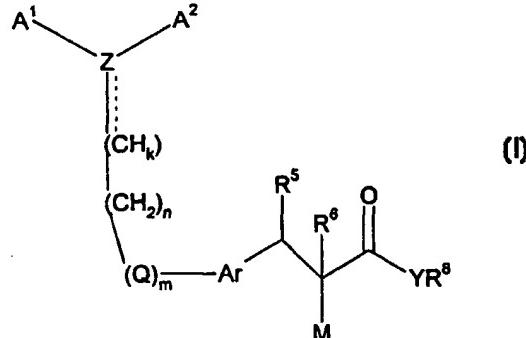
(51) International Patent Classification ⁷ :	A1	(11) International Publication Number: WO 00/63153
C07C 69/734, C07D 333/10, 213/24, 307/02, A61K 31/216, 31/381, 31/4402, 31/341, A61P 3/10, 3/04		(43) International Publication Date: 26 October 2000 (26.10.00)

(21) International Application Number: PCT/DK00/00190	(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 17 April 2000 (17.04.00)		
(30) Priority Data: PA 1999 00533 20 April 1999 (20.04.99) DK		
(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).		
(72) Inventors: MURRAY, Anthony; Esthersvej 32, 1. th., DK-2900 Hellerup (DK). SAUERBERG, Per; Syrenvænget 27, DK-3520 Farum (DK). JEPPESEN, Lone; Malmosevej 121, DK-2830 Virum (DK). PETTERSSON, Ingrid; Grundtvigsvej 18, 2. th., DK-1864 Frederiksberg (DK). BURY, Paul, Stanley; Hjortholms Allé 48, DK-2400 København NV (DK).	<p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: NEW COMPOUNDS, THEIR PREPARATION AND USE

(57) Abstract

The present invention relates to compounds of general formula (I). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).



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New Compounds, their Preparation and UseFIELD OF INVENTION

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The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

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BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

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The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

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Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous

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differentiation process throughout life. Much evidence points to the central role of PPAR γ activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose 5 metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of 10 free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the 15 phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in 20 rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to 25 changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid -oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

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A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. WO91/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

SUMMARY OF THE INVENTION

Glucose lowering as a single approach does not overcome the macrovascular complications
 5 associated with Type 2 diabetes and metabolic syndrome. Novel treatments of Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

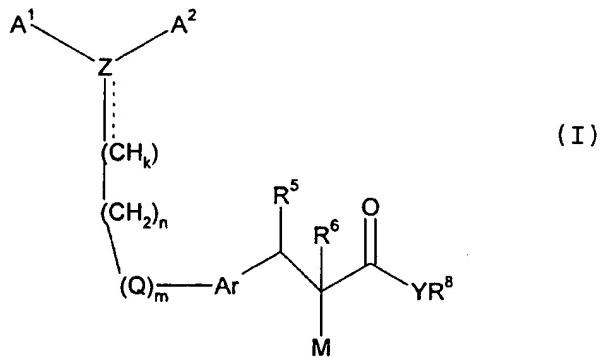
The clinical activity of fibrates and thiazolidinediones indicates that research for compounds
 10 displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of Type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

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DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I):

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wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen,
 25 perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclil, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy,

- acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, amino, acylamino, C₁₋₁₂-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, arylthio, C₁₋₁₂-alkylthio, thioC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, -COR¹, or -SO₂R², wherein R¹ and R² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- 10 Z is C, CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- 15 20 Q is O, S, NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₁₂-alkyl, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- 25 30 ----- represents a single bond or a double bond;
- Ar represents arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl, amino, hydroxy, C₁₋₆-alkoxy or aryl;

R⁵ represents hydrogen, hydroxy, halogen, C₁₋₁₂-alkoxy, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R⁵ forms a bond together with R⁶;

- 5 R⁶ represents hydrogen, hydroxy, halogen, C₁₋₁₂-alkoxy, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R⁶ forms a bond together with R⁵;

- M represents OR⁷, where R⁷ represents hydrogen, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, aryloxycarbonyl, C₁₋₁₂-alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocycl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or M represents COYR⁸;

- 15 R⁸ represents hydrogen, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocycl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 20 Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₁₂-alkyl, aryl, hydroxyC₁₋₁₂-alkyl or arylalkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl;

k is an integer ranging from 1 to 2, n is an integer ranging from 0 to 3 and m is an integer ranging from 0 to 1;

- 25 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- In a preferred embodiment, the present invention is concerned with compounds of
30 formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆-alkyl,

C₁₋₆-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

- 5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆-alkyl, C₁₋₆-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.
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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or aryl.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or aryl.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is a carbon atom at the end of a double bond, or Z is CR³, wherein R³ is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O, S, or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₆-alkyl, aminoC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, or perhalomethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O, S or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, aryl, arylalkyl, heteroarylalkyl, or acyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O or S.

- 5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is O.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene or heteroarylene, or a

- 10 divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl or C₁₋₆-alkoxy.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene, or heteroarylene.

- 15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene.

- In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl or arylalkyl optionally substituted with one or more halogen, or perhalomethyl or R⁵ forms a bond together with R⁶.

- 25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, or perhalomethyl or R⁵ forms a bond together with R⁶.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, halogen or R⁵ forms a bond together with R⁶.

- 30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen or perhalomethyl or R⁶ forms a bond together with R⁵.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen, halogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.

- 10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ represents hydrogen.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR⁷, where R⁷ represents hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, aryloxycarbonyl, C₁₋₆-alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or

- 20 heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR⁷, where R⁷ represents hydrogen, C₁₋₆-alkyl, C₄₋₆-

- 25 alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, or perhalomethyl.

- 30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR⁷, where R⁷ represents C₁₋₆-alkyl, or M represents COYR⁸.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein M represents OR⁷, where R⁷ represents ethyl, or M represents COYR⁸.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocycl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocycl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, or perhalomethyl.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen or C₁₋₆-alkyl.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen, methyl or ethyl.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₆-alkyl, aryl, hydroxyC₁₋₆-alkyl or arylalkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₆-alkyl, aryl, or arylalkyl groups, or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein k is an integer ranging from 1 to 2.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n and m are 1.

Preferred compounds of the invention are:

- 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,
- 5 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid,
- 3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 10 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,
- 2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid,
- 2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,
- 15 2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid,
- 3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
- 3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid,
- 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester,
- 2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid,
- 20 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid,
- 2-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-benzyl}-malonic acid dimethyl ester,
- (E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
- 25 (E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
- (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
- (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
- 30 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- 3-{4-[3,3-Bis-(3-methyl-thiophen-2-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
- 3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
- 2-Ethoxy-3-{4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl}-propionic acid ethyl ester,

- 2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid,
(*E, Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl}-propionic acid ethyl ester,
(*E, Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl}-propionic acid,
5 acid,
 (*E, Z*)-(2*S*)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester,
 (*E, Z*)-(2*S*)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid,
 (2*S*)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (2*S*)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
10 (Z)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl es-
 ter,
 (Z)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
 (*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl es-
 ter,
15 (*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
 (2*S*)-3-[4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (2*S*)-3-[4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid,
 (2*S*)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
 (2*S*)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
20 (Z)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 (Z)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl
 ester,
 (Z)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (2*S*)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
25 (2*S*)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
 (2*S*)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
 (2*S*)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (Z)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl
 ester,
30 (Z)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
 (*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl
 ester,
 (*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
 (2*S*)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

(2S)-3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid,

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,

- 5 (E, Z)-(2R)- 3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

10

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The term "C_{1-n}-alkyl" wherein n' can be from 2 through 12, as used herein, represents a

- 15 branched or straight or cyclic alkyl group having from one to the specified number of carbon atoms. Examples of such groups include, but are not limited to methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and the like and cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

- 20 The terms "C_{2-n}-alkenyl" wherein n' can be from 3 through 15, as used herein, represents an olefinically unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl and the like.

25

The terms "C_{2-n}-alkynyl" wherein n' can be from 3 through 15, as used herein, represents an unsaturated branched or straight hydrocarbon group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

30

The terms "C_{4-n}-alkenynyl" wherein n' can be from 5 through 15, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-

- 35 hexadiene-5-yne and the like.

The term "C₁₋₁₂-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₁₂-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples

- 5 of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy and the like. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.

- 10 The term "C₁₋₁₂-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio
15 and the like.

- The term "C₁₋₁₂-alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino,
20 propylamino, butylamino, pentylamino and the like. Examples of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and the like.

- The term "hydroxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl, 1-hydroxypropyl,
25 2-hydroxypropyl and the like.

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenylamino, naphthylamino and the like.

- 30 The term "arylalkylamino" as used herein, alone or in combination, refers to an arylalkyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-(1-naphthyl)ethylamino and the like.

The term "aminoC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached an amino group, e.g. aminoethyl, 1-aminopropyl, 2-aminopropyl and the like.

5

The term "aryloxycarbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. phenoxy carbonyl, 1-naphthyoxy carbonyl or 2-naphthyoxy carbonyl and the like.

10 The term "arylalkoxycarbonyl" as used herein, alone or in combination, refers to an arylalkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphthyl)ethoxycarbonyl and the like.

15 The term "C₁₋₁₂-alkoxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached a C₁₋₁₂-alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like.

20 The term "aryloxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g. phenoxy methyl, phenoxydodecyl, 1-naphthyoxyethyl, 2-naphthyoxypropyl and the like.

25 The term "arylalkoxyC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached an arylalkoxy as defined herein, e.g. benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphthyl)ethoxymethyl and the like.

30 The term "thioC₁₋₁₂-alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂-alkyl as defined herein whereto is attached a group of formula -SR'" wherein R''' is hydrogen, C₁₋₆-alkyl or aryl, e.g. thiomethyl, methylthiomethyl, phenylthioethyl and the like.

The term "C₁₋₁₂-alkoxycarbonylamino" as used herein, alone or in combination, refers to a C₁₋₁₂-alkoxycarbonyl as defined herein linked through amino having a free valence bond from

the nitrogen atom e.g. methoxycarbonylamino, carbethoxyamino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino and the like.

- The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an
5 aryloxycarbonyl as defined herein linked through amino having a free valence bond from the
nitrogen atom e.g. phenoxy carbonylamino, 1-naphthyoxy carbonylamino or 2-
naphthyoxy carbonylamino and the like.

- The term "arylalkoxycarbonylamino" as used herein, alone or in combination, refers to an
10 arylalkoxycarbonyl as defined herein linked through amino having a free valence bond from
the nitrogen atom e.g. benzyloxycarbonylamino, phenethoxycarbonylamino, 3-
phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-
naphthyl)ethoxycarbonylamino and the like.

- 15 The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected
from the group consisting of phenyl, naphthyl, (1-naphthyl or 2-naphthyl) and the like optionally
substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy and the like.

- 20 The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic
rings selected from the group consisting of phenylene, naphthylene and the like optionally
substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

- 25 The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or
triiodomethyl.

- The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two
hydrogen atoms independently are substituted with a straight or branched, saturated
30 hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-
ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-
pentyl)amino and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl and the like.

- 5 The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. acetoxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy and the like.
- 10 The term "C₁₋₁₂-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₁₂-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxy carbonyl and the like.
- 15 The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole,
- 20 quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine and the like.

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic

- 25 aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine and the like.

30

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline,

quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen, and the like.

- The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain
5 containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyoxy, 2-naphthyoxy and the like.

10

The term "arylalkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

- 15 The term "heteroarylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

- 20 The term "heteroarylalkoxy" as used herein refers to a heteroarylalkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen, and the like.

- 25 The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino and the like.

- 30 The term "(C₃₋₆-cycloalkyl)C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C₃₋₆-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl and the like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g.

- 5 phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio and the like.

The term "C₁₋₆-alkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-

- 10 butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl and the like.

- 15 As used herein, the phrase "heterocycl" means a monovalent saturated or unsaturated non aromatic group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocycl" includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone and the like); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine and the like); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine and the like); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms, and the like.

- As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone and the like); 5-membered heterocycles having three het-

eroatoms (e.g. tetrahydrofuran and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine and the like); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine and the like); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four
5 heteroatoms, and the like.

- As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes,
10 but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 1,4-dioxolanyl and the like, 5-membered heterocycles having one hetero atom (e.g.
15 thiophenes, pyrroles, furans and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines and the like); 5-membered heterocycles having three heteroatoms (e.g. triazoles, thiadiazoles and the like); 5-membered heterocycles having four heteroatoms; 6-membered
20 heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine and the like); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, quinazolines, morpholines and the like); 6-membered heterocycles with three heteroatoms (e.g. 1,3,5-triazine and the like); and 6-membered heterocycles with four heteroatoms and the like.
25 As used herein, the phrase "a 9-10 membered bicyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 9-10 membered bicyclic ring" includes but is not limited to naphthalene, quinoline, isoquinoline, indole, benzothiophene, benzofuran and the like.
30 Certain of the above defined terms may occur more than once in the above formula (I), and upon such occurrence each term shall be defined independently of the other.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as 5 organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, 10 bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthalates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable 15 salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic 20 bases include lysine, arginine, guanidine, diethanolamine, choline and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

- The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula I may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the dia-stereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.
- Various polymorphs of compound of general formula I forming part of this invention may be prepared by crystallization of compound of formula I under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.
- The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmaceutical substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

Furthermore, the present compounds of formula I can be utilised in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

- 5 In a further aspect, the present invention relates to a method of treating and/or preventing Type I or Type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of Type I or Type II diabetes.

10 In a still further aspect, the present compounds are useful for the treatment and/or prevention of IGT.

- 15 In a still further aspect, the present compounds are useful for the treatment and/or prevention of Type 2 diabetes.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from IGT to Type 2 diabetes.

20

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

- 25 In another aspect, the present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity.

30 In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance (Type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders.

In still another aspect, the present compounds are effective in decreasing apoptosis in mammalian cells such as beta cells of Islets of Langerhans.

In still another aspect, the present compounds are useful for the treatment of certain renal
5 diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis.

In still another aspect, the present compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome
10 (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

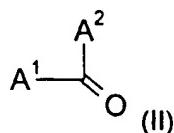
The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.
15

Furthermore, the invention relates to the use of compounds of the general formula I or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions mediated by nuclear receptors,
20 in particular the Peroxisome Proliferator-Activated Receptors (PPAR) such as the conditions mentioned above.

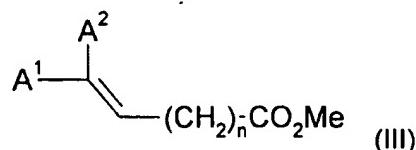
The present invention also relates to a process for the preparation of the above said novel
25 compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

The method comprises:

30
a) Reacting a compound of formula (II) where A¹ and A² are as defined previously with a phosphonate ester in a Horner Emmons reaction



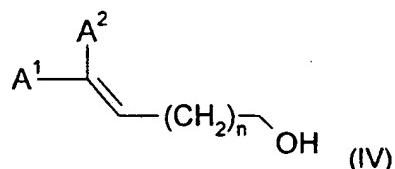
to give a compound of formula III where A^1 and A^2 and n are as defined previously.



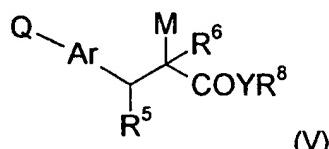
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whereupon a compound of formula III can be reduced with diisobutyl aluminium hydride to give a compound of formula IV where A^1 and A^2 and n are as defined previously. Alternatively a compound of formula IV can be prepared via reaction of a compound of formula II with $(Ph_3P)_3PCH_2(CH_2)_nCH_2OH\cdot Br$ and $BuLi$ in a Wittig reaction

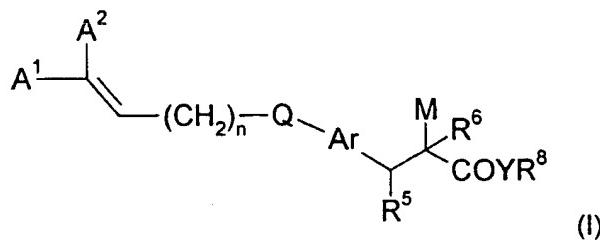
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The alcohol group in a compound of formula IV can undergo a Mitsunobo reaction with a compound of formula V, alternatively it can be converted to a suitable leaving group (mesy-15 loxy, halide) and react under alkylating conditions with a compound of formula V, wherein Q is OH, SH or amino, Ar, M, Y and R^5-R^8 are as defined previously.



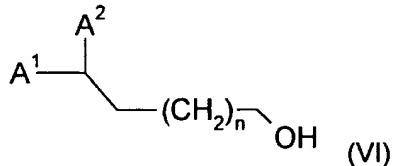
to give a compound of formula I, wherein $k=1$ and A^1 , A^2 , Q , Ar , M , Y , n and R^5-R^8 are as defined previously.



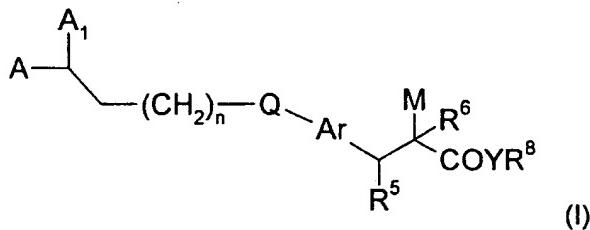
Ester deprotection of a compound of formula (I) can be carried out using standard hydrolysis techniques, to give a compound of formula I, wherein Y is O, k=1 and A¹, A², Q, Ar, M, n and R⁵-R⁸ are as defined previously.

5

Hydrogenating a compound of formula IV under palladium catalysis to give a compound of formula VI wherein A¹ and A² and n are as defined previously:



- 10 A compound of formula VI can undergo a Mitsunobo reaction with a compound of formula V to give a compound of formula I, wherein k=2 and A¹, A², Q, Ar, M, Y, n and R⁵-R⁸ are as defined previously.



- 15 Ester deprotection of a compound of formula (I) can be carried out using standard hydrolysis techniques, to give a compound of formula I, wherein Y is O, k=2 and A¹, A², Q, Ar, M, n and R⁵-R⁸ are as defined previously.

PHARMACOLOGICAL METHODS

20

In vitro PPAR alpha and PPAR gamma activation activity.

Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from 5 the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid 10 contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The 15 amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

Methods

20 Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluence of 80 % at transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

25

Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPAR α : aa 167 - C-term; PPAR γ : aa 165 - C-term) and fused to GAL4-DBD by subcloning 30 fragments in frame into the vector pM1 generating the plasmids pM1 α LBD and pM1 γ LBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 µl growth medium including de-lipidated serum) for 24 h followed by luciferase assay.

- 5 Luciferase assay: Medium including test compound was aspirated and 100 µl PBS incl. 1mM Mg⁺⁺ and Ca⁺⁺ was added to each well. The luciferase assay was performed using the Lu-
cLite kit according to the manufacturers instructions (Packard Instruments). Light emission
was quantified by counting SPC mode on a Packard Instruments top-counter.

10

PHARMACEUTICAL COMPOSITIONS

- In another aspect, the present invention includes within its scope pharmaceutical compositions
15 comprising, as an active ingredient, at least one of the compounds of the general formula I or a
pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or
diluent.

- The present compounds may also be administered in combination with one or more further
20 pharmacologically active substances eg., selected from antiobesity agents, antidiabetics, an-
tihypertensive agents, agents for the treatment and/or prevention of complications resulting
from or associated with diabetes and agents for the treatment and/or prevention of complica-
tions and disorders resulting from or associated with obesity.

- 25 Thus, in a further aspect of the invention the present compounds may be administered in
combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine
regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4)
30 agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin re-
leasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists,
urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH
(melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin
re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and

noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

10

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

15 In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as
20 those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides,
25 meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such
30 as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sul-

- 5 phonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg. metformin.

- 10 In yet another embodiment the present compounds are administered in combination with a meglitinide eg. repaglinide.

In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg. miglitol or acarbose.

- 15 In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

- 20 Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

- 25 In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

- 30 Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and

ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

5

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

10

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

15

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions,

20 conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active
25 compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid
30 monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring

agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

- 5 The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
5 Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.

Coating:

10 HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

15 The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

20 The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to 25 begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

30 Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonary or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

5

Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES

10

The process for preparing compounds of formula I, and preparations containing them, is further illustrated in the following examples, which however, are not to be construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (δ) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in °C. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

Abbreviations:

TLC:	thin layer chromatography
DMSO:	dimethylsulfoxide
CDCl ₃ :	deuterated chloroform
DMF:	N,N-dimethylformamide
min:	minutes
h:	hours

30

Example 1

(E,Z)-2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester

To a solution of 3-phenyl-3-(4-methyl-phenyl)-prop-2-en-1-ol (150mg, 0.6mmol), triphenyl-phosphine (195mg, 0.73mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (190mg, 0.79mmol) in THF at ice bath temperature was added diethylazodicarboxylate (0.11mL, 0.73mmol) and the reaction stirred 1.5h at this temperature and 16h at room temperature. Ice water was added and the crude product isolated by a dichloromethane extraction and brine wash. Concentration under reduced pressure and flash chromatography gave the title compound (300mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.28 (6H, 2xCH₃), 2.30 and 2.40 (3H, CH₃), 2.90-2.93 (2H, CH₂), 3.30-3.40 and 3.51-3.61 (2H, OCH₂), 3.90-4.0 (1H, CHCO₂), 4.10-4.19 (2H, OCH₂), 4.41-4.61 (2H, OCH₂) 6.23-6.32 (1H, CHalkene), 6.70-6.81 (2H, aryl), 7.03-7.45 (remaining H, aryl).

MS calcd for C₂₉H₃₂O₄ 444.6, Found 444.2

15

Example 2

(E,Z)-2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid

(E,Z)-2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 1) (80mg, 0.18mmol) was hydrolysed in 1N NaOH (0.35mL) and ethanol (0.35mL) for 4 h at room temperature and 16h at 5°C. Water (1mL) was added and the reaction mixture was neutralised with 6N HCl. The crude product was extracted with dichloromethane and concentrated under reduced pressure. Flash chromatography gave the title compound (48mg).
25

¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.20 (3H, CH₃), 2.32 and 2.40 (3H, CH₃), 2.85-3.10 (2H, CH₂), 3.30-3.45 and 3.51-3.68 (2H, OCH₂), 3.95-4.06 (1H, CHCO₂), 4.51-4.61 (2H, OCH₂) 6.21-6.41 (1H, CHalkene), 6.72-6.82 (2H, aryl), 7.03-7.50 (remaining H, aryl).

MS calcd for C₂₇H₂₈O₄ 416.5, Found 416.3.

30

Example 3

(E, Z)-3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

To a solution of 3-(2-chloro-phenyl)-3-phenyl-prop-2-en-1-ol (370mg, 1.5mmol), tributyl-phosphine (0.5mL, 1.6mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380mg, 1.6mmol) in benzene at ice bath temperature was added azodicarboxylic dipiperidine (403mg, 1.6mmol) and the reaction stirred 1h. Work up and purification as for Example 1 gave the title compound (490mg).

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.30 (6H, 2xCH₃), 2.90-2.95 (2H, CH₂), 3.29-3.40 and 3.52-3.63 (2H, OCH₂), 3.90-4.0 (1H, CHCO₂), 4.10-4.20 (2H, OCH₂), 4.35-4.56 and 4.70-4.80 (2H, OCH₂), 6.00-6.08 and 6.42-6.53 (1H, CHalkene), 6.70-6.81 (2H, aryl), 7.06-7.55 (remaining H, aryl).

MS calcd for C₂₈H₂₉ClO₄ 465.0, Found 464.2.

Example 4

15

(E, Z)-3-[4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl]-2-ethoxy-propionic acid

20 (E, Z)-3-[4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 3) (400mg, 0.86mmol) was hydrolysed in an identical manner to example 2 to give the title compound (353mg).

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.09-1.20 (3H, CH₃), 2.85-3.10 (2H, CH₂), 3.30-3.42 and 3.51-3.65 (2H, OCH₂), 3.96-4.05 (1H, CHCO₂), 4.35-4.50 and 4.70-4.74 (2H, OCH₂) 6.00-6.05 and 6.42-6.49 (1H, CHalkene), 6.71-6.82 (2H, aryl), 7.05-7.50 (remaining H, aryl).

25 MS calcd for C₂₆H₂₅ClO₄ 436.9, Found 436.2.

Example 5

3-[4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

30

Reaction of 3, 3-bis(4-methoxy-phenyl)-prop-2-en-1-ol (216mg, 0.8mmol), triphenyl-phosphine (240mg, 0.9mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (240mg, 1.0 mmol) and diethylazodicarboxylate (0.11mL, 0.9mmol) in an identical manner to Example 1 gave the title compound (90mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.30 (6H, 2xCH₃), 2.90-2.95 (2H, CH₂), 3.29-3.39 and 3.52-3.65 (2H, OCH₂), 3.78 (3H, OCH₃), 3.82 (3H, OCH₃), 3.90-3.99 (1H, CHCO₂), 4.10-4.20 (2H, OCH₂), 4.51-4.59 (1H, OCH₂) 6.12-6.19 (1H, CHalkene), 6.70-7.45 (remaining H, aryl).

5

MS calcd for C₃₀H₃₄O₆ 490.6, Found 488.3.

Example 6

10 3-[4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid

3-[4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 5) (80mg, 0.16mmol) was hydrolysed in an identical manner to example 2 to give the title compound (29mg).

15

¹H NMR (CDCl₃, 300 MHz); δ 1.12-1.20 (3H, CH₃), 2.87-3.09 (2H, CH₂), 3.32-3.49 and 3.52-3.63 (2H, OCH₂), 3.78 (3H, OCH₃), 3.82 (3H, OCH₃), 3.99-4.02 (1H, CHCO₂), 4.51-4.55 (1H, OCH₂) 6.12-6.19 (1H, CHalkene), 6.72-7.23 (remaining H, aryl).

MS calcd for C₂₈H₃₀O₆ 462.5, Found 462.1

20

Example 7

(E, Z)-3-[4-[3-phenyl-3-(Biphenyl-4-yl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

25 Reaction of 3-phenyl-3-(biphenyl-4-yl)-prop-2-en-1-ol (250mg, 0.66mmol), triphenylphosphine (195mg, 0.73mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (190mg, 0.79 mmol) and diethylazodicarboxylate (0.11mL, 0.79mmol) in an identical manner to Example 1 gave the title compound (180mg).

30 ¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.32 (6H, 2xCH₃), 2.89-2.95 (2H, CH₂), 3.28-3.39 and 3.52-3.63 (2H, OCH₂), 3.91-3.96 (1H, CHCO₂), 4.08-4.20 (2H, OCH₂), 4.51-4.62 (1H, OCH₂) 6.29-6.41 and 6.61-6.70 (1H, CHalkene), 6.72-7.80 (2H, aryl), 7.08-7.18 (2H, aryl), 7.20-7.70 (remaining H, aryl).

MS calcd for C₃₄H₃₄O₄ 506.6, Found 504.2.

Example 8(E, Z)-3-{4-[3-phenyl-3-(Biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

5

(E, Z)-3-{4-[3-phenyl-3-(Biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 7) (70mg, 0.13mmol) was hydrolysed in an identical manner to example 2 to give the title compound (25mg).

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.02-1.23 (3H, CH₃), 2.83-3.12 (2H, CH₂), 3.32-3.50 and 3.52-3.63 (2H, OCH₂), 3.96-4.07 (1H, CHCO₂), 4.51-4.70 (1H, OCH₂) 6.39-6.41 (1H, CHalkene), 6.72-7.82 (2H, aryl), 7.01-7.65 (remaining H, aryl).

MS calcd for C₃₂H₃₀O₄ 478.6, Found 478.2

15

Example 9(E, Z)-2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester

Reaction of 3-phenyl-3-(thiophen-2-yl)-prop-2-en-1-ol (320mg, 1.5mmol), tributylphosphine (0.4mL, 1.6mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380mg, 1.6mmol) and azodicarboxylic dipiperidine(403mg, 1.6mmol) in an identical manner to Example 3 gave the title compound (290mg).

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.08-1.32 (6H, 2xCH₃), 2.90-2.99 (2H, CH₂), 3.28-3.39 and 3.52-3.63 (2H, OCH₂), 3.91-3.99 (1H, CHCO₂), 4.08-4.21 (2H, OCH₂), 4.42-4.50 and 4.72-4.80 (1H, OCH₂), 6.19-6.25 and 6.32-6.39 (1H, CHalkene), 6.62-7.48 (remaining H, aryl).

MS calcd for C₂₆H₂₈O₄S 436.6, Found 436.1.

Example 10

30

(E, Z)-2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid

(E, Z)-2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 9) (200mg, 0.45mmol) was hydrolysed in an identical manner to example 2 to give the title compound (94mg).

5 ^1H NMR (CDCl_3 , 300 MHz); δ 1.12-1.31 (3H, CH_3), 2.88-3.10 (2H, CH_2), 3.28-3.48 and 3.52-3.58 (2H, OCH_2), 3.96-4.03 (1H, CHCO_2), 4.42-4.48 and 4.76-4.80 (1H, OCH_2), 6.19-6.22 and 6.32-6.39 (1H, CHalkene), 6.65-7.48 (remaining H, aryl).

MS calcd for $\text{C}_{24}\text{H}_{24}\text{O}_4\text{S}$ 408.5, Found 408.2.

10

Example 112-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester

Reaction of 3-phenyl-3-(pyridin-2-yl)-prop-2-en-1-ol (320mg, 1.5mmol), tributylphosphine (0.42mL, 1.6mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380mg, 1.6mmol) and azodicarboxylic dipiperide (403mg, 1.6mmol) in an identical manner to Example 3 gave the title compound (650mg).

20 ^1H NMR (CDCl_3 , 300 MHz); δ 1.10-1.30 (6H, 2x CH_3), 2.90-2.95 (2H, CH_2), 3.28-3.39 and 3.51-3.62 (2H, OCH_2), 3.90-3.95 (1H, CHCO_2), 4.05-4.20 (2H, OCH_2), 4.53-4.59 (1H, OCH_2) 6.72-6.78 (1H, CHalkene), 6.95-7.60 (remaining H, aryl and pyridyl), 8.58-8.61 (1H, pyridyl).

MS calcd for $\text{C}_{27}\text{H}_{29}\text{O}_4\text{N}$ 431.5, Found 431.3.

25

Example 122-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid

2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester (example 30 11) (210mg, 0.48mmol) was hydrolysed in an identical manner to example 2 to give the title compound (110mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.18 (3H, CH₃), 2.82-3.04 (2H, CH₂), 3.28-3.39 and 3.51-3.62 (2H, OCH₂), 3.92-3.97 (1H, CHCO₂), 4.53-4.65 (1H, OCH₂) 6.70-6.78 (1H, CHalkene), 6.88-7.62 (remaining H, aryl and pyridyl), 8.58-8.62 (1H, pyridyl).

MS calcd for C₂₅H₂₅O₄N 403.5, Found 403.2.

5

Example 13

3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

10 Reaction of 3, 3-diphenyl-propan-1-ol (110mg, 0.5mmol), triphenylphosphine (145mg, 0.55mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (140mg, 0.6 mmol) and diethylazodicarboxylate (0.09mL, 0.55mmol) in an identical manner to Example 1 gave the title compound (120mg).

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.29 (6H, 2xCH₃), 2.44-2.55 (2H, CH₂), 2.90-2.95 (2H, CH₂), 3.28-3.39 and 3.51-3.62 (2H, OCH₂), 3.80-3.89 (2H, CH₂), 3.90-3.95 (1H, CHCO₂), 4.10-4.28 (3H, arylCH and OCH₂), 6.70-6.77 (2H, aryl), 7.05-7.35 (remaining H, aryl).
MS calcd for C₂₈H₃₂O₄ 432.6, Found 432.3.

20

Example 14

3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid

3-[4-(3, 3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 13) (110mg, 0.25mmol) was hydrolysed in an identical manner to example 2 to give the title compound (55mg).

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.19 (3H, CH₃), 2.42-2.55 (2H, CH₂), 2.87-3.08 (2H, CH₂), 3.30-3.47 and 3.51-3.62 (2H, OCH₂), 3.80-3.89 (2H, CH₂), 3.98-4.03 (1H, CHCO₂), 4.10-4.25 (1H, arylCH), 6.70-6.77 (2H, aryl), 7.05-7.35 (remaining H, aryl).
MS calcd for C₂₆H₂₈O₄ 404.5, Found 404.3.

Example 15

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester

Reaction of 3-phenyl-3-(4-methylphenyl)-2-propan-1-ol (210mg, 0.88mmol), tributyl-phosphine (0.25mL, 1.0mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (240mg, 1.0mmol) and azodicarboxylic dipiperide (250mg, 1.0mmol) in an identical manner to Example 3 gave the title compound (160mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.28 (6H, 2xCH₃), 2.29 (3H, CH₃), 2.42-2.49 (2H, CH₂), 2.89-2.93 (2H, CH₂), 3.25-3.40 and 3.51-3.61 (2H, OCH₂), 3.88-3.85 (2H, CH₂), 3.90-4.00 (1H, CHCO₂), 4.10-4.19 (3H, arylCH and OCH₂), 6.69-6.73 (2H, aryl), 7.03-7.29 (remaining H, aryl).
MS calcd for C₂₉H₃₄O₄ 446.6, Found 446.3.

Example 16

15

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester (example 15) (130mg, 0.30mmol) was hydrolysed in an identical manner to example 2 to give the title compound (55mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.11-1.21 (3H, CH₃), 2.29 (3H, CH₃), 2.42-2.53 (2H, CH₂), 2.83-3.12 (2H, CH₂), 3.38-3.50 and 3.51-3.63 (2H, OCH₂), 3.80-3.88 (2H, CH₂), 3.99-4.05 (1H, CHCO₂), 4.12-4.22 (1H, arylCH), 6.69-6.73 (2H, aryl), 7.03-7.29 (remaining H, aryl).
MS calcd for C₂₇H₃₀O₄ 418.5, Found 418.3.

Example 173-{4-[3-phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

30

Reaction of 3-biphenyl-4-yl-3-phenyl-propan-1-ol (145mg, 0.5mmol), triphenylphosphine (145mg, 0.55mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (140mg, 0.6 mmol) and diethylazodicarboxylate (0.09mL, 0.55mmol) in an identical manner to Example 1 gave the title compound (230mg).

¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.28 (6H, 2xCH₃), 2.48-2.55 (2H, CH₂), 2.89-2.93 (2H, CH₂), 3.25-3.40 and 3.51-3.63 (2H, OCH₂), 3.88-4.00 (3H, CH₂ and CHCO₂), 4.10-4.19 (2H, OCH₂), 4.20-4.30 (1H, CH), 6.67-6.71 (2H, aryl), 7.05-7.55 (remaining H, aryl).

5 MS calcd for C₃₄H₃₆O₄ 508.7, Found 508.3.

Example 18

3-[4-[3-phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl]-2-ethoxy-propionic acid

10

3-[4-[3-phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 17) (200mg, 0.39mmol) was hydrolysed in an identical manner to example 2 to give the title compound (70mg).

15

¹H NMR (CDCl₃, 300 MHz); δ 1.07-1.20 (3H, CH₃), 2.49-2.61 (2H, CH₂), 2.88-3.09 (2H, CH₂), 3.32-3.48 and 3.51-3.66 (2H, OCH₂), 3.88-3.92 (2H, CH₂) 3.95-4.05 (1H, CHCO₂), 4.20-4.30 (1H, CH), 6.67-6.79 (2H, aryl), 7.05-7.55 (remaining H, aryl).

MS calcd for C₃₂H₃₂O₄ 480.6, Found 480.3.

20

Example 19

2-[4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-benzyl]-malonic acid dimethyl ester

25

Under a nitrogen atmosphere, 3,3-bis-(4-methoxy-phenyl)-prop-2-en-1-ol (500 mg, 1.95 mmol), tributylphosphine (424 (mg, 2.1 mmol) and 2-(4-hydroxy-benzyl)-malonic acid dimethyl ester (464 mg, 1.95 mmol) were successively dissolved in dry benzene (50 mL). Solid azodicarboxylic dipiperidine (ADDP) (530 mg, 2.1 mmol) was added under stirring at 0°C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. Heptane (10 mL) was added to the reaction mixture and di hydro-ADDP separated out was filtered off. After evaporation of the solvent the product was purified by chromatography eluting with heptane/ethylacetate (4:1) to give 150 mg (16%) of the title compound.

¹H NMR (CDCl₃, 300 MHz); δ 3.15 (2H, PhCH₂), 3.63 (1H, CH), 3.70 (6H, 2xCO₂CH₃), 3.80 (3H, PhOCH₃), 3.83 (3H, PhOCH₃), 4.55 (1H, OCH₂), 6.15 (1H, CHalkene), 6.70-7.20 (remaining H, aryl).

5

Example 20(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester

- 10 Reaction of (E)-3-(4-furan-2-yl-phenyl)-3-phenyl-prop-2-en-1-ol (475 mg, 1.72 mmol), tributylphosphine (0.63 ml, 2.58 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (451 mg, 1.89 mmol) and azodicarboxylic dipiperidide (650 mg, 2.58 mmol) in benzene in an identical manner to example 3 gave the title compound (450 mg, 53%).
- 15 ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.26-3.40 (1H, m), 3.52-3.64 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.58 (2H, d), 6.36 (1H, t), 6.47 (1H, dd), 6.63 (1H, d), 6.77 (2H, dm), 7.12 (2H, dm), 7.16-7.31 (4H, m), 7.31-7.50 (4H, m), 7.58 (2H, dm).

20

Example 21(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

- 25 (E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 20) (440 mg, 0.89 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (408 mg, 97%)

30 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.93 (1H, dd), 3.07 (1H, dd), 3.39-3.52 (1H, m), 3.52-3.64 (1H, m), 4.04 (1H, dd), 4.58 (2H, d), 6.36 (1H, t), 6.48 (1H, m), 6.63 (1H, d), 6.79 (2H, dm), 7.12 (2H, dm), 7.16-7.32 (4H, m), 7.32-7.50 (4H, m), 7.59 (2H, dm), COOH too broad to be observed.

LCMS (electrospray): 491 (M+Na), 259 (100%).

Example 22

(E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of (E)-3-biphenyl-4-yl-3-phenyl-prop-2-en-1-ol (1.0 g, 3.49 mmol), tributylphosphine (1.3 ml, 5.24 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.92 g, 3.84 mmol) and azodicarboxylic dipiperidine (1.32 g, 5.24 mmol) in benzene in an identical manner to example 3 gave the title compound (1.47 g, 83%).

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.95 (2H, d), 3.28-3.40 (1H, m), 3.53-3.65 (1H, m), 3.95 (1H, t), 4.15 (2H, q), 4.57 (2H, d), 6.39 (1H, t), 6.78 (2H, dm), 7.12 (2H, dm), 7.20-7.48 (10H, m), 7.48-7.62 (4H, m).

Example 23

15 (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid
16 (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester
example 22 (1.38 g, 2.72 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (1.25 mg, 96%)
20 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.95 (1H, dd), 3.06 (1H, dd), 3.37-3.52 (1H, m), 3.52-3.64 (1H, m), 4.03 (1H, dd), 4.59 (2H, d), 6.38 (1H, t), 6.78 (2H, m), 7.12 (2H, dm), 7.20-7.49 (10H, m), 7.49-7.62 (4H, m), COOH too broad to be observed.

Example 24

25 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester
26 Reaction of (E, Z)-3-biphenyl-4-yl-3-phenyl-prop-2-en-1-ol (601 mg, 2.1 mmol), triphenylphosphine (606 mg, 2.31 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (601 mg, 2.52 mmol) and diethyl lazodicarboxylate (402 mg, 2.31 mmol) in an identical manner to example 1 gave the title compound (400 mg, 38%).

¹H NMR (CDCl₃, 200 MHz); δ 1.10-1.30 (6H, m), 2.94 (2H, d), 3.25-3.45 (1H, m), 3.50-3.65 (1H, m), 3.96 (1H, t), 4.16 (2H, dd), 4.55-4.68 (2H, d), 6.30-6.44 (1H, m), 6.73-6.84 (2H, m), 7.14 (2H, dm), 7.20-7.70 (14H, m).

5

Example 25(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

10 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 24) (400 mg, 0.79 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (250 mg, 66%)

15 ¹H NMR (CDCl₃, 300 MHz); δ 1.05-1.20 (3H, m), 2.94 (1H, dd), 3.01 (1H, dd), 3.30-3.43 (1H, m), 3.50-3.68 (1H, m), 4.00 (1H, dd), 4.50-4.68 (2H, m), 6.27-6.40 (1H, m), 6.72-6.84 (2H, m), 7.12 (2H, dm), 7.18-7.65 (14H, m), 9.85 (1H, br s).

Example 263-[4-[3,3-Bis-(3-methyl-thiophen-2-yl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

20

Reaction of 3,3-bis-(3-methylthiophen-2-yl)-prop-2-en-1-ol (1.0 mg, 3.99 mmol), tributyl-phosphine (0.91 g, 4.5 mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.07 g, 4.5 mmol) and azodicarboxylic dipiperidine (1.14 g, 4.5 mmol) in an identical manner to example 3 gave the title compound (680 mg, 36%).

25

¹H NMR (CDCl₃, 200 MHz); δ 1.15 (3H, t), 1.23 (3H, t), 2.00 (3H, s), 2.08 (3H, s), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.50-3.64 (1H, m), 3.94 (1H, t), 4.14 (2H, dd), 4.58 (2H, d), 6.24 (1H, t), 6.70-6.81 (3H, m), 6.88 (1H, d), 7.04-7.15 (3H, m), 7.21-7.30 (1H, m).

30

Example 273-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-(4-bromophenyl)-prop-2-en-1-ol (0.50 g, 1.36 mmol), triphenylphosphine (0.39 g, 1.50 mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.39 g, 1.63 mmol) and diethyl azodicarboxylate (0.26 g, 1.51 mmol) in an identical manner to example 1 gave the title compound (450 mg, 56%).

5

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.22 (3H, t), 2.94 (2H, d), 3.28-3.42 (1H, m), 3.53-3.65 (1H, m), 3.96 (1H, t), 4.16 (2H, q), 4.52 (2H, d), 6.32 (1H, t), 6.75 (2H, dm), 7.01-7.20 (6H, m), 7.43 (2H, dm), 7.52 (2H, dm).

MS (EI): 586/588/590 (M⁺), 513/515/517, 349/351/353 (100%).

10

Example 28

3-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid

15 3-[4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 27) (150 mg, 0.25 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (135 mg, 96%)

20 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.94 (1H, dd), 3.06 (1H, dd), 3.40-3.52 (1H, m), 3.52-3.66 (1H, m), 4.04 (1H, dd), 4.51 (2H, d), 6.30 (1H, t), 6.76 (2H, dm), 7.00-7.20 (6H, m), 7.42 (2H, dm), 7.52 (2H, dm), COOH too broad to be observed.

MS (EI): 558/560/562 (M⁺), 349/351/353, 270/272 (100%), 191.

Example 29

25

2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester

30 Reaction of 3-phenyl-3-pyridin-4-yl-prop-2-en-1-ol (0.50 g, 2.37 mmol), triphenylphosphine (0.68 g, 2.61 mmol), 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.68 g, 2.84 mmol) and diethyl azodicarboxylate (0.46 g, 2.63 mmol) in an identical manner to example 1 gave the title compound (435 mg, 43%).

¹H NMR (CDCl₃, 200 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.94 (2H, d), 3.25-3.43 (1H, m), 3.50-3.70 (1H, m), 3.98 (1H, t), 4.17 (2H, q), 4.52 (2H, d), 6.41 (1H, t), 6.76 (2H, dm), 7.05-7.40 (9H, m), 8.66 (2H, dm).

MS (EI): 431 (M⁺), 194 (100%).

5 Mp. 84-87°C

Example 30

2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid

10

2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester (example 29) (200 mg, 0.46 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (50 mg, 27%)

15

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 2.98 (1H, dd), 3.06 (1H, dd), 3.33-3.49 (1H, m), 3.60-3.75 (1H, m), 4.03 (1H, dd), 4.52 (2H, d), 6.46 (1H, t), 6.78 (2H, dm), 7.09-7.40 (9H, m), 8.63 (2H, dm), 9.23 (1H, br s).

Example 31

20

(E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid ethyl ester

25

Reaction of 3-(4-methoxyphenyl)-3-thiophen-2-yl-prop-2-en-1-ol (271 mg, 1.10 mmol), triphenylphosphine (289 mg, 1.10 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (238 mg, 1.0 mmol) and diethyl azodicarboxylate (188 mg, 1.08 mmol) in an identical manner to example 1 gave the title compound (80 mg, 17%).

30

¹H NMR (CDCl₃, 200 MHz); δ 1.10-1.28 (6H, m), 2.88-2.98 (2H, m), 3.25-3.43 (1H, m), 3.47-3.69 (1H, m), 3.77-3.90 (3H, m), 3.95 (1H, tm), 4.16 (2H, q), 4.45-4.78 (2H, m), 6.10-6.48 (1H, m), 6.70-7.50 (11H, m).

Example 32

(E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid

5 (E, Z)-(2S)-2-Ethoxy-3-[4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl]-propionic acid ethyl ester (example 31) (75 mg, 0.16 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (40 mg, 57%)

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.83-3.13 (2H, m), 3.27-3.50 (1H, m), 3.50-3.70 (1H, m), 3.77-3.88 (3H, m), 3.97-4.09 (1H, m), 4.43-4.28 (2H, m), 6.10-6.30 (1H, m), 6.70-7.40 (11H, m), COOH too broad to be observed.

MS (EI): 438 (M⁺), 229 (100%).

Example 33

15 (E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester

Reaction of (E, Z)-3-phenyl-3-tolyl-prop-2-en-1-ol (841 mg, 3.75 mmol), triphenylphosphine (1.03 g, 3.93 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (851 mg, 3.57 mmol) and diethyl lazodicarboxylate (656 mg, 3.94 mmol) in an identical manner to example 1 gave the title compound (0.64 g, 40%).

10 ¹H NMR (CDCl₃, 300 MHz); δ 1.14 (3H, t), 1.22 (3H, t), 2.30-2.42 (3H, m), 2.93 (2H, d), 3.26-3.40 (1H, m), 3.51-3.66 (1H, m), 3.94 (1H, t), 4.16 (2H, q), 4.49-4.63 (2H, m), 6.20-6.33 (1H, m), 6.76 (2H, dm), 7.00-7.45 (11H, m).

25 MS (EI): 444 (M⁺), 207 (100%).

Example 34

(E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid

30 (E, Z)-(2S)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester (example 33) (0.55 g, 1.24 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (0.50 g, 97%)

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.24-2.41 (3H, m), 2.93 (1H, dd), 3.04 (1H, dd), 3.37-3.64 (2H, m), 4.03 (1H, dd), 4.50-4.63 (2H, m), 6.20-6.32 (1H, m), 6.78 (2H, dm), 7.00-7.43 (11H, m), COOH too broad to be observed.

MS (EI): 416 (M⁺), 207 (100%).

5

Example 35

(2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

- 10 Reaction of 3,3-diphenyl-prop-2-en-1-ol (210 mg, 1.0 mmol), tributylphosphine (303 mg, 1.50 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (250 mg, 1.05 mmol) and azodicarboxylic dipiperide (378 mg, 1.50 mmol) in an identical manner to example 3 gave the title compound (290 mg, 67%).
- 15 ¹H NMR (CDCl₃, 300 MHz); δ 1.14 (3H, t), 1.21 (3H, t), 2.92 (2H, d), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.56 (2H, d), 6.31 (1H, t), 6.75 (2H, dm), 7.10 (2H, dm), 7.16-7.44 (10H, m).

Example 36

20

(2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

- 25 (2S)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 35) (215 mg, 0.50 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (180 mg, 90%)

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.93 (1H, dd), 3.04 (1H, dd), 3.38-3.50 (1H, m), 3.50-3.63 (1H, m), 4.03 (1H, dd), 4.58 (2H, d), 6.31 (1H, t), 6.77 (2H, dm), 7.11 (2H, dm), 7.17-7.43 (10H, m), COOH too broad to be observed.

30

Example 37

(Z)-(2S)-2-Ethoxy-3-[4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl]-propionic acid ethyl ester

Reaction of (*Z*)-3-(4-fluorophenyl)-3-phenyl-prop-2-en-1-ol (200 mg, 0.88 mmol), triphenylphosphine (242 mg, 0.92 mmol), (2*S*)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (200 mg, 0.84 mmol) and diethyl azodicarboxylate (160 mg, 0.92 mmol) in an identical manner to example 1 gave the title compound (275 mg, 73%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.27-3.40 (1H, m), 3.51-3.65 (1H, m), 3.96 (1H, t), 4.14 (2H, q), 4.54 (2H, d), 6.33 (1H, t), 6.76 (2H, dm), 6.95-7.40 (11H, m).

MS (EI): 448 (M⁺), 375, 211 (100%).

Example 38

(Z)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

(*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 37) (200 mg, 0.45 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (158 mg, 86%)

¹H NMR (CDCl₃, 200 MHz); δ 1.15 (3H, t), 2.84-3.14 (2H, m), 3.35-3.68 (2H, m), 4.04 (1H, dd), 4.54 (2H, d), 6.32 (1H, t), 6.77 (2H, dm), 7.00-7.40 (11H, m), COOH too broad to be observed.

MS (EI): 420 (M⁺), 368, 317, 211 (100%).

Example 39

(E)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester

Reaction of (*E*)-3-(4-fluorophenyl)-3-phenyl-prop-2-en-1-ol (200 mg, 0.88 mmol), triphenylphosphine (242 mg, 0.92 mmol), (2*S*)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (200 mg, 0.84 mmol) and diethyl azodicarboxylate (160 mg, 0.92 mmol) in an identical manner to example 1 gave the title compound (320 mg, 85%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.24-3.43 (1H, m), 3.50-3.67 (1H, m), 3.96 (1H, t), 4.16 (2H, q), 4.54 (2H, d), 6.25 (1H, t), 6.75 (2H, dm), 6.90-7.03 (2H, m), 7.03-7.30 (6H, m), 7.30-7.45 (3H, m).

MS (EI): 448 (M⁺), 375, 211 (100%).

5

Example 40

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

10 (E)-(2S)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 39) (225 mg, 0.50 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (245 mg, 95%)

15 ¹H NMR (CDCl₃, 200 MHz); δ 1.17 (3H, t), 2.83-3.14 (2H, m), 3.34-3.68 (2H, m), 4.02 (1H, dd), 4.53 (2H, d), 6.24 (1H, t), 6.78 (2H, dm), 6.89-7.05 (2H, m), 7.05-7.49 (9H, m), COOH too broad to be observed.

MS (EI): 420 (M⁺), 317, 211 (100%).

Example 41

20

(2S)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-(4-methoxyphenyl)-prop-2-en-1-ol (1.62 g, 5.99 mmol), triphenyl-phosphine (2.88 g, 10.98 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.19 g, 4.99 mmol) and diethyl lazodicarboxylate (1.92 g, 11.04 mmol) in an identical manner to example 1 gave the title compound (0.434 g, 17%).

30 ¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.27-3.41 (1H, m), 3.53-3.65 (1H, m), 3.80 (3H, s), 3.84 (3H, s), 3.95 (1H, t), 4.15 (2H, q), 4.56 (2H, d), 6.17 (1H, t), 6.71-6.87 (4H, m), 6.92 (2H, dm), 7.05-7.25 (6H, m).

Example 42

(2S)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

(2S)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 41) (225 mg, 0.495 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (150 mg, 71%)

5

¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.95 (1H, dd), 3.04 (1H, dd), 3.38-3.50 (1H, m), 3.52-3.66 (1H, m), 3.80 (3H, s), 3.83 (3H, s), 4.03 (1H, dd), 4.57 (2H, d), 6.17 (1H, t), 6.71-6.85 (4H, m), 6.92 (2H, dm), 7.05-7.25 (6H, m), COOH too broad to be observed.

10

Example 43(2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-di-(4-methylphenyl)-prop-2-en-1-ol (1.0 g, 4.20 mmol), tributylphosphine (1.27 g, 6.30 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.10 g, 4.62 mmol) and azodicarboxylic dipiperidine (1.59 g, 6.30 mmol) in an identical manner to example 3 gave the title compound (0.76 g, 39%).

¹H NMR (CDCl₃, 300 MHz); δ 1.13 (3H, t), 1.21 (3H, t), 2.33 (3H, s), 2.38 (3H, s), 2.93 (2H, d), 3.26-3.41 (1H, m), 3.52-3.66 (1H, m), 3.95 (1H, t), 4.15 (2H, q), 4.56 (2H, d), 6.27 (1H, t), 6.75 (2H, dm), 7.00-7.21 (10H, m).
MS (EI): 458 (M⁺), 385, 221 (100%).

Example 44

25

(2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(2S)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 43) (0.76 g, 1.66 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (0.696 g, 98%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 2.33 (3H, s), 2.38 (3H, s), 2.94 (1H, dd), 3.05 (1H, dd), 3.39-3.51 (1H, m), 3.51-3.65 (1H, m), 4.03 (1H, dd), 4.57 (2H, d), 6.23 (1H, t), 6.77 (2H, dm), 7.00-7.22 (10H, m), COOH too broad to be observed.

MS (EI): 430 (M^+), 327, 221 (100%).

Example 45

5 (Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of (Z)-3-biphenyl-4-yl-3-phenyl-prop-2-en-1-ol (171 mg, 0.60 mmol), triphenylphosphine (142 mg, 0.63 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (149 mg, 0.63 mmol) and diethyl azodicarboxylate (95 mg, 0.55 mmol) in an identical 10 manner to example 1 gave the title compound (160 mg, 53%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.95 (1H, t), 4.14 (2H, q), 4.63 (2H, d), 6.33 (1H, t), 6.78 (2H, dm), 7.12 (2H, dm), 7.20-7.50 (10H, m), 7.55-7.68 (4H, m).

15

Example 46

(Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

20 (Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 45) (0.36 g, 0.71 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (0.345 g, 86%) as an orange gum containing approximately 0.6 molar equivalents of ethyl acetate.

25 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 1.26 (1.8H, t, ethyl acetate), 2.04 (1.8H, s, ethyl acetate), 2.95 (1H, dd), 3.06 (1H, dd), 3.38-3.52 (1H, m), 3.52-3.64 (1H, m), 4.03 (1H, dd), 4.12 (1.2H, q, ethyl acetate), 4.63 (2H, d), 6.32 (1H, t), 6.80 (2H, dm), 7.11 (2H, dm), 7.20-7.50 (10H, m), 7.54-7.68 (4H, m), COOH too broad to be observed.

MS (EI): 478 (M^+), 375, 269 (100%).

30

Example 47

(Z)-(2S)-3-[4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of 3-(4-bromophenyl)-3-phenyl-prop-2-en-1-ol (145 mg, 0.50 mmol), triphenylphosphine (144 mg, 0.55 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (119 mg, 0.50 mmol) and diethyl azodicarboxylate (96 mg, 0.55 mmol) in an identical manner to example 1 gave the title compound (110 mg, 43%).

- ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 1.21 (3H, t), 2.94 (2H, d), 3.29-3.41 (1H, m), 3.53-3.65 (1H, m), 3.96 (1H, t), 4.15 (2H, q), 4.53 (2H, d), 6.32 (1H, t), 6.75 (2H, dm), 7.05-7.18 (4H, m), 7.18-7.38 (5H, m), 7.52 (2H, dm).
- MS (EI): 508/510 (M+) 435/437, 393/395, 271/273, 192 (100%).
- Microanalysis for C₂₈H₂₉BrO₄ + 0.1 H₂O: calculated = 65.78%C, 5.76%H; found 65.79%C, 5.91%H.

Example 48

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(Z)-(2S)-3-[4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl]-2-ethoxy-propionic acid

(Z)-(2S)-3-[4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 47) (90 mg, 0.18 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (60 mg, 71%).

- ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.96 (1H, dd), 3.05 (1H, dd), 3.39-3.51 (1H, m), 3.51-3.64 (1H, m), 4.03 (1H, dd), 4.52 (2H, d), 6.32 (1H, t), 6.75 (2H, dm), 7.02-7.18 (4H, m), 7.18-7.40 (5H, m), 7.51 (2H, dm), COOH too broad to be observed.
- LCMS (electrospray): 503/505 (M+Na), 498/500 (M+NH₄), 271/273 (100%).

Example 49

(2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of 3,3-bis-biphenyl-4-yl-prop-2-en-1-ol (363 mg, 1.0 mmol), tributylphosphine (303 mg, 1.5 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.1

mmol) and azodicarboxylic dipiperide (378 mg, 1.5 mmol) in an identical manner to example 3 gave the title compound (445 mg, 76%) containing 0.8 equivalents of ethyl acetate.

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 1.25 (2.4H, t, ethyl acetate), 2.04 (2.4H, s, ethyl acetate), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.51-3.65 (1H, m), 3.96 (1H, t), 4.07-4.20 ({2H, q} plus {1.6H, q, ethyl acetate}), 4.54 (2H, d), 6.40 (1H, t), 6.80 (2H, dm), 7.03 (2H, dm), 7.27-7.70 (18H, m).

Example 50

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(2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(2S)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (example 49) (560 mg, 0.96 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (450 mg, 84%).

¹H NMR (CDCl₃, 300 MHz); δ 1.13 (3H, t), 2.93 (1H, dd), 3.05 (1H, dd), 3.35-3.50 (1H, m), 3.50-3.64 (1H, m), 4.02 (1H, dd), 4.62 (2H, d), 6.39 (1H, t), 6.80 (2H, dm), 7.02 (2H, dm), 7.27-7.72 (18H, m), COOH too broad to be observed.

20

Example 51

(2S)-3-[4-(3,3-Bis-(4-bromophenyl)-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

25 Reaction of 3,3-bis-(4-bromophenyl)-prop-2-en-1-ol (2.60 g, 7.0 mmol), tributylphosphine (2.52 g, 10.0 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.50 g, 6.3 mmol) and azodicarboxylic dipiperide (2.02 g, 10.0 mmol) in an identical manner to example 3 gave the title compound (2.8 g, 75%).

30 ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.27-3.40 (1H, m), 3.53-3.65 (1H, m), 3.94 (1H, t), 4.15 (2H, q), 4.51 (2H, d), 6.31 (1H, t), 6.75 (2H, dm), 7.01-7.19 (6H, m), 7.42 (2H, dm), 7.52 (2H, dm).

Example 52(2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid

- 5 (2S)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 51) (2.8 g, 4.76 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (2.3 g, 83%) which contained approximately 0.25 molar equivalents of ethyl acetate.
- 10 ^1H NMR (CDCl_3 , 300 MHz); δ 1.15 (3H, t), 1.25 (0.75H, t, ethyl acetate), 2.04 (0.75H, s, ethyl acetate), 2.93 (1H, dd), 3.04 (1H, dd), 3.37-3.49 (1H, m), 3.52-3.68 (1H, m), 4.02 (1H, dd), 4.12 (0.5H, q, ethyl acetate), 4.50 (2H, d), 6.30 (1H, t), 6.74 (2H, dm), 7.00-7.19 (6H, m), 7.49 (2H, dm), 7.50 (2H, dm), COOH too broad to be observed.

15

Example 53(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester

- 20 Reaction of (Z)-3-(4-furan-2-yl-phenyl)-3-phenyl-prop-2-en-1-ol (300 mg, 1.09 mmol), tributylphosphine (0.40 ml, 1.64 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (286 mg, 1.20 mmol) and azodicarboxylic dipiperide (413 mg, 1.64 mmol) in benzene in an identical manner to example 3 gave the title compound (260 mg, 48%).
- 25 ^1H NMR (CDCl_3 , 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.60 (2H, d), 6.30 (1H, t), 6.49 (1H, dd), 6.69 (1H, d), 6.77 (2H, dm), 7.11 (2H, dm), 7.18-7.32 (7H, m), 7.49 (1H, d), 7.69 (2H, dm).
LCMS (electrospray): 519 (M+Na), 514 (M+NH₄), 259 (100%).

30

Example 54(Z)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid

(*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester (example 53) (240 mg, 0.483 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (170 mg, 75%).

5

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 2.93 (1H, dd), 3.05 (1H, dd), 3.33-3.49 (1H, m), 3.50-3.65 (1H, m), 4.01 (1H, dd), 4.60 (2H, d), 6.30 (1H, t), 6.49 (1H, dd), 6.68 (1H, d), 6.78 (2H, dm), 7.11 (2H, dm), 7.15-7.36 (7H, m), 7.49 (1H, d), 7.68 (2H, dm), COOH too broad to be observed.

10 LCMS (electrospray): 491 (M+Na), 486 (M+NH₄), 259 (100%).

Example 55

(*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester

Reaction of (*E*)- 3-(4-bromophenyl)-3-phenyl-prop-2-en-1-ol (289 mg, 1.0 mmol), tributyl-phosphine (0.37 ml, 1.5 mmol), (2*S*)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.10 mmol) and azodicarboxylic dipiperidide (378 mg, 1.5 mmol) in benzene in 20 an identical manner to example 3 gave the title compound (460 mg, 90%).

¹H NMR (CDCl₃, 300 MHz); δ 1.15 (3H, t), 1.21 (3H, t), 2.92 (2H, d), 3.26-3.40 (1H, m), 3.51-3.65 (1H, m), 3.94 (1H, t), 4.15 (2H, q), 4.54 (2H, d), 6.29 (1H, t), 6.74 (2H, dm), 7.03-7.45 (11H, m).

25 LCMS (electrospray): 531/533 (M+Na), 271/273 (100%).

Example 56

(*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid

30

(*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester (example 55) (382 mg, 0.75 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (350 mg, 97%).

¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 2.93 (1H, dd), 3.05 (1H, dd), 3.38-3.50 (1H, m), 3.50-3.63 (1H, m), 4.03 (1H, dd), 4.53 (2H, d), 6.30 (1H, t), 6.75 (2H, dm), 7.03-7.45 (11H, m), COOH too broad to be observed.

LCMS (electrospray): 503/505 (M+Na), 498/500 (M+NH₄), 271/273 (100%).

5

Example 57

(2S)-3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester

- 10 Reaction of 3,3-bis-(4-furan-2-yl-phenyl)-prop-2-en-1-ol (460 mg, 1.34 mmol), tributyl-phosphine (0.50 ml, 2.0 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (320 mg, 1.34 mmol) and azodicarboxylic dipiperidine (504 mg, 2.0 mmol) in benzene in an identical manner to example 3 gave the title compound (541 mg, 72%).
- 15 ¹H NMR (CDCl₃, 300 MHz); δ 1.16 (3H, t), 1.21 (3H, t), 2.93 (2H, d), 3.28-3.40 (1H, m), 3.51-3.64 (1H, m), 3.94 (1H, t), 4.14 (2H, q), 4.59 (2H, d), 6.35 (1H, t), 6.40-6.51 (2H, m), 6.62 (1H, d), 6.69 (1H, d), 6.77 (2H, dm), 7.13 (2H, dm), 7.20-7.33 (4H, m), 7.44 (1H, d), 7.48 (1H, d), 7.58 (2H, dm), 7.70 (2H, m).

20

Example 58

(2S)-3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid

- 25 (2S)-3-[4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid ethyl ester (example 57) (530 mg, 0.95 mmol) was hydrolysed in an identical manner to example 2 to give the title compound (400 mg, 79%).

- 30 ¹H NMR (CDCl₃, 300 MHz); δ 1.17 (3H, t), 2.95 (1H, dd), 3.07 (1H, dd), 3.40-3.52 (1H, m), 3.52-3.63 (1H, m), 4.05 (1H, dd), 4.60 (2H, d), 6.35 (1H, t), 6.44-6.51 (2H, m), 6.64 (1H, d), 6.70 (1H, d), 6.79 (2H, dm), 7.12 (2H, dm), 7.20-7.34 (4H, m), 7.47 (1H, d), 7.50 (1H, d), 7.59 (2H, dm), 7.70 (2H, dm), COOH too broad to be observed.

Example 59

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

Reaction of (E, Z)-3-biphenyl-4-yl-3-p-tolyl-prop-2-en-1-ol (300 mg, 1.0 mmol), tributyl-

phosphine (0.37 ml, 1.5 mmol), (2S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl es-

- 5 ter (262 mg, 1.10 mmol) and azodicarboxylic dipiperidide (378 mg, 1.50 mmol) in benzene in
an identical manner to example 3 gave the title compound (390 mg, 76%).

¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.25 (6H, m), 2.30-2.42 (3H, m), 2.92 (2H, d), 3.27-3.40
(1H, m), 3.50-3.65 (1H, m), 3.94 (1H, tm), 4.13 (2H, qm), 4.57-4.64 (2H, m), 6.23-6.38 (1H,

10 m), 6.79 (2H, dm), 7.03-7.67 (15H, dm).

LCMS (electrospray): 543 (M+Na), 538 (M+NH₄), 283 (100%).

Example 60

- 15 (E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester
(example 59) (370 mg, 0.71 mmol) was hydrolysed in an identical manner to example 2 to
give the title compound (310 mg, 89%).

20

¹H NMR (CDCl₃, 300 MHz); δ 1.10-1.22 (3H, m), 2.30-2.44 (3H, m), 2.93 (1H, dd), 3.04 (1H,
dd), 3.37-3.63 (2H, m), 3.98-4.07 (1H, m), 4.54-4.65 (2H, m), 6.25-6.38 (1H, m), 6.79 (2H,
dm), 7.02-7.67 (15H, m), COOH too broad to be observed.

LCMS (electrospray): 515 (M+Na), 283 (100%).

25

Example 61

(E, Z)-(2R)- 3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl es-
ter

30

Potassium carbonate (0.25 g, 1.81 mmol) was added to a stirred solution of 4-(3-bromo-1-
phenyl-prop-1-enyl)-biphenyl (0.35 g, 1.00 mmol) and (2R)-2-ethoxy-3-(4-hydroxy-phenyl)-
propionic acid ethyl ester (0.215 g, 0.90 mmol) in dry acetone (20 ml), and the mixture
heated to 60°C under reflux for 18 h. The resulting suspension was cooled to room tempera-

ture, filtered to remove inorganic products, and the solvents evaporated. The product was purified by flash column chromatography on silica gel, eluting with 15% ethyl acetate in light petroleum, to give the title compound as a colourless gum (0.40 g, 87%).

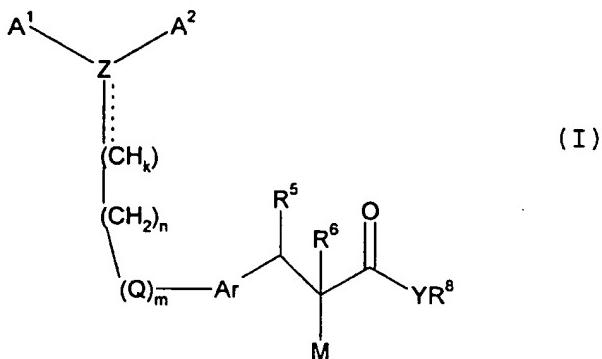
- 5 ¹H NMR (CDCl₃, 300 MHz); δ 1.09-1.32 (6H, m), 2.93 (2H, d), 3.27-3.41 (1H, m), 3.51-3.67 (1H, m), 3.96 (1H, t), 4.18-4.20 (2H, m), 4.52-4.68 (2H, m), 6.28-6.41 (1H, m), 6.72-6.83 (2H, m), 7.12 (2H, dm), 7.18-7.69 (14H, m).

10

15

CLAIMS:

1. A compound of formula (I)



5

- wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂-alkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, 10 C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, amino, acylamino, C₁₋₁₂-alkyl-amino, C₁₋₆-dialkylamino, arylamino, arylalkylamino, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, 15 aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, arylthio, C₁₋₁₂-alkylthio, thioC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, -COR¹, or -SO₂R², wherein R¹ and R² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, 20 perhalomethyl, hydroxy, nitro or cyano;

Z is C, CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or

aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Q is O, S, NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl,

- 5 C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₁₂-alkyl, aminoC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

----- represents a single bond or a double bond;

- 15 Ar represents arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl, amino, hydroxy, C₁₋₆-alkoxy or aryl;

- 20 R⁵ represents hydrogen, hydroxy, halogen, C₁₋₁₂-alkoxy, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R⁵ forms a bond together with R⁶;

- 25 R⁶ represents hydrogen, hydroxy, halogen, C₁₋₁₂-alkoxy, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or R⁶ forms a bond together with R⁵;

- 30 M represents OR⁷, where R⁷ represents hydrogen, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxycarbonyl, aryloxycarbonyl, C₁₋₁₂-alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano or M represents COYR⁸;

R⁸ represents hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, arylalkyl, heterocycll, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 5 Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₁₂alkyl, aryl, hydroxyC₁₋₁₂alkyl or arylalkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆alkyl;

- 10 k is an integer ranging from 1 to 2, n is an integer ranging from 0 to 3 and m is an integer ranging from 0 to 1;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- 15 2. A compound according to claim 1 wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆alkyl, (C₃₋₆-cycloalkyl)C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycll, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyl-amino, C₁₋₆dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆alkyl, C₁₋₆alkoxycarbonyl, alkylaminocarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆alkoxyC₁₋₆alkyl, aryloxyC₁₋₆alkyl, or arylalkoxyC₁₋₆alkyl.
- 20 3. A compound according to any one of the preceding claims wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆alkyl, (C₃₋₆-cycloalkyl)C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycll, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyl-amino, C₁₋₆dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, aryloxyC₁₋₆alkyl, or arylalkoxyC₁₋₆alkyl.
- 25 4. A compound according to any one of the preceding claims wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆alkyl, (C₃₋₆-cycloalkyl)C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycll, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyl-amino, C₁₋₆dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, aryloxyC₁₋₆alkyl, or arylalkoxyC₁₋₆alkyl.
- 30 5. A compound according to any one of the preceding claims wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, C₁₋₆alkyl, (C₃₋₆-cycloalkyl)C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocycll, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyl-amino, C₁₋₆dialkylamino, arylamino, arylalkylamino, aminoC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, aryloxyC₁₋₆alkyl, or arylalkoxyC₁₋₆alkyl.

4. A compound according to any one of the preceding claims wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring or a 9-10 membered bicyclic ring, optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or aryl.
5. A compound according to any one of the preceding claims wherein A¹ and A² are independently of each other a 5-6 membered cyclic ring optionally substituted with one or more halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or aryl.
6. A compound according to any one of the preceding claims wherein Z is a carbon atom at
10 the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₁₂-alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₁₂-alkyl, C₁₋₁₂-alkoxyC₁₋₁₂-alkyl, aryloxyC₁₋₁₂-alkyl, arylalkoxyC₁₋₁₂-alkyl, thioC₁₋₁₂-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino
15 optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
7. A compound according to any one of the preceding claims wherein Z is a carbon atom at
20 the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC₁₋₆-alkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR⁴, or -SO₂R¹¹, wherein R⁴ and R¹¹ independently of each
25 other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
8. A compound according to any one of the preceding claims wherein Z is a carbon atom at
30 the end of a double bond, or Z is CR³, wherein R³ is hydrogen, halogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, or arylalkoxyC₁₋₆-alkyl.
9. A compound according to any one of the preceding claims wherein Z is a carbon atom at
the end of a double bond, or Z is CR³, wherein R³ is hydrogen.

10. A compound according to any one of the preceding claims wherein Q is O, S, or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, acyl, hydroxyC₁₋₆-alkyl, aminoC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C₁₋₆-alkoxyC₁₋₆-alkyl, aryloxyC₁₋₆-alkyl, arylalkoxyC₁₋₆-alkyl, thioC₁₋₆-alkyl, -COR¹³, or -

- 5 SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆-alkoxy or amino optionally substituted with one or more C₁₋₆-alkyl, perhalomethyl or aryl optionally substituted with one or more halogen, or perhalomethyl.

10

11. A compound according to any one of the preceding claims wherein Q is O, S, or NR¹², wherein R¹² is hydrogen, perhalomethyl, C₁₋₆-alkyl, aryl, arylalkyl, heteroarylalkyl, or acyl.

12. A compound according to any one of the preceding claims wherein Q is O or S.

15

13. A compound according to any one of the preceding claims wherein Q is O.

14. A compound according to any one of the preceding claims wherein ----- represents a single bond or a double bond.

20 15. A compound according to any one of the preceding claims wherein Ar represents arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C₁₋₆-alkyl or C₁₋₆-alkoxy.

25 16. A compound according to any one of the preceding claims wherein Ar represents arylene, or heteroarylene.

17. A compound according to any one of the preceding claims wherein Ar represents arylene.

30 18. A compound according to any one of the preceding claims wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl or arylalkyl optionally substituted with one or more halogen, or perhalomethyl or R⁵ forms a bond together with R⁶.

19. A compound according to any one of the preceding claims wherein R⁵ represents hydrogen, halogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, or perhalomethyl or R⁵ forms a bond together with R⁶.
- 5 20. A compound according to any one of the preceding claims wherein R⁵ represents hydrogen, halogen or R⁵ forms a bond together with R⁶.
21. A compound according to any one of the preceding claims wherein R⁵ represents hydrogen.
- 10 22. A compound according to any one of the preceding claims wherein R⁶ represents hydrogen, C₁₋₆-alkoxy, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, acyl or arylalkyl optionally substituted with one or more halogen or perhalomethyl or R⁶ forms a bond together with R⁵.
- 15 23. A compound according to any one of the preceding claims wherein R⁶ represents hydrogen, halogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.
24. A compound according to any one of the preceding claims wherein R⁶ represents hydrogen, C₁₋₆-alkoxy, or R⁶ forms a bond together with R⁵.
- 20 25. A compound according to any one of the preceding claims wherein R⁶ represents hydrogen.
26. A compound according to any one of the preceding claims wherein M represents OR⁷, where R⁷ represents hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, aryalkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, aryloxycarbonyl, C₁₋₆-alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
- 30 27. A compound according to any one of the preceding claims wherein M represents OR⁷, where R⁷ represents hydrogen, C₁₋₆-alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, aryalkyl, C₁₋₆-alkoxyC₁₋₆-alkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen or perhalomethyl.

28. A compound according to any one of the preceding claims wherein M represents OR⁷, where R⁷ represents C₁₋₆-alkyl or M represents COYR⁸ where R⁸ is defined as in claim 1.
29. A compound according to any one of the preceding claims wherein M represents OR⁷, where R⁷ represents ethyl or M represents COYR⁸ where R⁸ is defined as in claim 1.
30. A compound according to any one of the preceding claims wherein R⁸ represents hydrogen, C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
31. A compound according to any one of the preceding claims wherein R⁸ represents hydrogen, C₁₋₆alkyl, C₄₋₆-alkenynyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups optionally substituted with one or more halogen, or perhalomethyl.
32. A compound according to any one of the preceding claims wherein R⁸ represents hydrogen or C₁₋₆alkyl.
33. A compound according to any one of the preceding claims wherein R⁸ represents hydrogen or ethyl.
34. A compound according to any one of the preceding claims wherein Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₆-alkyl, aryl, hydroxyC₁₋₆-alkyl or arylalkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl.
35. A compound according to any one of the preceding claims wherein Y represents oxygen, or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₆-alkyl, aryl, or arylalkyl groups, or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆-alkyl.
36. A compound according to any one of the preceding claims wherein Y represents oxygen.

37. A compound according to any one of the preceding claims wherein k is an integer ranging from 1 to 2.

38. A compound according to any one of the preceding claims wherein n and m are 1.

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39. The compound according to claim 1, which is

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid ethyl ester,

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-allyloxy]-phenyl}-propionic acid,

10 3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

3-{4-[3-(2-Chloro-phenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

3-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

15 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,

2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,

2-Ethoxy-3-{4-[3-phenyl-3-(thiophen-2-yl)-allyloxy]-phenyl}-propionic acid,

2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid ethyl ester,

2-Ethoxy-3-{4-[3-phenyl-3-(pyridin-2-yl)-allyloxy]-phenyl}-propionic acid,

20 3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,

3-[4-(3,3-Diphenyl-propoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid ethyl ester,

2-Ethoxy-3-{4-[3-phenyl-3-(4-methylphenyl)-propoxy]-phenyl}-propionic acid,

3-{4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

25 3-{4-[3-Phenyl-3-(biphenyl-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid,

2-{4-[3,3-Bis-(4-methoxy-phenyl)-allyloxy]-benzyl}-malonic acid dimethyl ester,

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,

(E)-(2S)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,

30 (E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,

(E)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,

(E, Z)-(2S)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,

- 3-{4-[3,3-Bis-(3-methyl-thiophen-2-yl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
3-{4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid ethyl ester,
- 5 2-Ethoxy-3-[4-(3-phenyl-3-pyridin-4-yl-allyloxy)-phenyl]-propionic acid,
(*E, Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl}-propionic acid ethyl ester,
(*E, Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-methoxyphenyl)-3-thiophen-2-yl-allyloxy]-phenyl}-propionic acid,
- 10 (*E, Z*)-(2*S*)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid ethyl ester,
(*E, Z*)-(2*S*)-2-Ethoxy-3-[4-(3-phenyl-3-p-tolyl-allyloxy)-phenyl]-propionic acid,
(2*S*)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
(2*S*)-3-[4-(3,3-Diphenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
(*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl es-
- 15 ter,
(*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
(*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl es-
ter,
(*E*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-fluorophenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,
- 20 (2*S*)-3-{4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
(2*S*)-3-[4-[3,3-Bis-(4-methoxyphenyl)-allyloxy]-phenyl]-2-ethoxy-propionic acid,
(2*S*)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
(2*S*)-3-[4-(3,3-Di-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
(*Z*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- 25 (Z)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
(Z)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,
(2*S*)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl ester,
(2*S*)-3-[4-(3,3-Bis-biphenyl-4-yl-allyloxy)-phenyl]-2-ethoxy-propionic acid,
- 30 (2*S*)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,
(2*S*)-3-{4-[3,3-Bis-(4-bromophenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,
(*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid ethyl ester,
(*Z*)-(2*S*)-2-Ethoxy-3-{4-[3-(4-furan-2-yl-phenyl)-3-phenyl-allyloxy]-phenyl}-propionic acid,

(*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

(*E*)-(2*S*)-3-{4-[3-(4-Bromophenyl)-3-phenyl-allyloxy]-phenyl}-2-ethoxy-propionic acid,

(2*S*)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid ethyl ester,

5 (2*S*)-3-{4-[3,3-Bis-(4-furan-2-yl-phenyl)-allyloxy]-phenyl}-2-ethoxy-propionic acid,

(*E*, *Z*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl es-

ter,

(*E*, *Z*)-(2*S*)-3-[4-(3-Biphenyl-4-yl-3-p-tolyl-allyloxy)-phenyl]-2-ethoxy-propionic acid,

10 (10) (2*R*)-3-[4-(3-Biphenyl-4-yl-3-phenyl-allyloxy)-phenyl]-2-ethoxy-propionic acid ethyl es-

ter; or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

15 40. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

20 41. A composition according to claim 40 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

25 42. A pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

30 43. A pharmaceutical composition useful in the treatment and/or prevention of diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

44. A pharmaceutical composition according to any one of the claims 40-43 for oral, nasal, transdermal, pulmonary, or parenteral administration.
45. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 40-44.
46. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 40-44.
47. A method for the treatment and/or prevention of diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 40-44.
48. The method according to claims 45, 46 or 47, wherein the effective amount of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.
49. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.
50. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

51. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.

INTERNATIONAL SEARCH REPORT

International application No. PCT/DK 00/00190
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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 69/734, C07D 333/10, C07D 213/24, C07D 307/02, A61K 31/216, A61K 31/381, A61K 31/4402, A61K 31/341, A61P 3/10, A61P 3/04
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9919313 A1 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 22 April 1999 (22.04.99), page 1, line 24 - line 27; page 2, line 1 - line 6; page 37 - page 50, examples --	1-51
P,X	WO 9920614 A1 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 29 April 1999 (29.04.99), page 1, line 23 - line 28; page 2, line 1 - line 15; page 42 - page 76, examples --	1-51
P,X	WO 9938850 A1 (DR. REDDY'S RESEARCH FOUNDATION), 5 August 1999 (05.08.99), page 1, line 27 - line 28; page 2, line 1 - line 20; page 43 - page 66, EXAMPLES --	1-51

Further documents are listed in the continuation of Box C.

See patent family annex.

<ul style="list-style-type: none"> * Special categories of cited documents "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	<ul style="list-style-type: none"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search

18 August 2000

Date of mailing of the international search report

22-08-2000

Name and mailing address of the ISA,
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
 Facsimile No. + 46 8 666 02 86

Authorized officer
Nabil Gecer/ELY
 Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No. PCT/DK 00/00190	
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9908501 A2 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 25 February 1999 (25.02.99), page 1, line 20 - line 29; page 2, line 1 - line 15; page 50 - page 90, examples --	1-51
X	WO 9916758 A1 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 8 April 1999 (08.04.99), page 1, line 21 - line 28; page 2, line 1 - line 11; page 42 - page 62, examples --	1-51
X	EP 0903343 A1 (SSP CO., LTD.), 24 March 1999 (24.03.99), page 2, line 35 - line 43; page 24 - page 43, tables 1-20 --	1-51
X	WO 9604260 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96), page 2, line 1 - line 18; page 13 - page 25, examples --	1-51
X	WO 9604261 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96), page 2, line 1 - line 18; page 12 - page 24, examples --	1-51
X	WO 9725042 A1 (SMITHKLINE BEECHAM P.L.C.), 17 July 1997 (17.07.97), page 2, line 6 - line 21; page 18 - page 31, examples --	1-51
A	WO 9731907 A1 (GLAXO GROUP LIMITED), 4 Sept 1997 (04.09.97) --	1-51

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00190

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>STN International, File CAPLUS, CAPLUS accession no. 1998:430714, Document no. 129:108904, Mitsui Petrochemical Industries, LTD.: "Preparation of hydroxybenzoic acids, their use as cell adhesion inhibitors, and their pharmaceutical compositions"; & JP,A210182550, 19980707</p> <p>--</p> <p>-----</p>	1-51

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/DK00/00190**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **45-48**
because they relate to subject matter not required to be searched by this Authority, namely:
See extra sheet*
2. Claims Nos.: **1-38 , 40-51**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet**
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00190

*Claims 45-48 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**The claims are too broadly formulated to permit a meaningful search over the whole of the claimed scope. Furthermore, the claims are only partly supported by the examples given in the descriptive part of the application. Guided by the spirit of the application the search was carried out mainly on the basis of the exemplified compounds (PCT Art. 6)

INTERNATIONAL SEARCH REPORT

Information on patent family members				International application No. PCT/DK 00/00190	
Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
WO 9919313 A1	22/04/99	NONE			
WO 9920614 A1	29/04/99	AU 1120699 A	10/05/99		
WO 9938850 A1	05/08/99	NONE			
WO 9908501 A2	25/02/99	AU 1120599 A	08/03/99		
WO 9916758 A1	08/04/99	NONE			
EP 0903343 A1	24/03/99	CN 1215051 A JP 11158144 A	28/04/99 15/06/99		
WO 9604260 A1	15/02/96	AP 9700918 D AU 697545 B AU 1006199 A AU 3382695 A BG 101180 A BR 9508468 A CA 2196079 A CN 1158123 A CZ 9700254 A EP 0772605 A FI 970357 A GB 9415330 D HU 76637 A IL 114759 D IL 125525 D JP 10503508 T NO 970373 A NZ 292125 A PL 318766 A SK 12297 A TR 960096 A WO 9604261 A GB 9425599 D GB 9509923 D GB 2289999 A GB 9501323 D	00/00/00 08/10/98 04/03/99 04/03/96 30/04/98 25/11/97 15/02/96 27/08/97 17/09/97 14/05/97 26/03/97 00/00/00 28/10/97 00/00/00 00/00/00 31/03/98 18/03/97 25/11/98 07/07/97 06/08/97 00/00/00 15/02/96 00/00/00 00/00/00 06/12/95 00/00/00		

INTERNATIONAL SEARCH REPORT

Information on patent family members			02/12/99	International application No. PCT/DK 00/00190
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9604261 A1	15/02/96	AP 9700918 D AU 697545 B AU 1006199 A AU 3382695 A BG 101180 A BR 9508468 A CA 2196079 A CN 1158123 A CZ 9700254 A EP 0772605 A FI 970357 A GB 9415330 D HU 76637 A IL 114759 D IL 125525 D JP 10503508 T NO 970373 A NZ 292125 A PL 318766 A SK 12297 A TR 960096 A WO 9604260 A GB 9425599 D GB 9509923 D		00/00/00 08/10/98 04/03/99 04/03/96 30/04/98 25/11/97 15/02/96 27/08/97 17/09/97 14/05/97 26/03/97 00/00/00 28/10/97 00/00/00 00/00/00 31/03/98 18/03/97 25/11/98 07/07/97 06/08/97 00/00/00 15/02/96 00/00/00 00/00/00
WO 9725042 A1	17/07/97	AP 9801272 D AU 1439797 A AU 4839196 A BG 102668 A BR 9706968 A CA 2242632 A CN 1212622 A CZ 9802163 A EP 0815091 A EP 0879053 A GB 9600464 D HU 9900560 A IL 125106 D JP 10511977 T NO 974170 A NO 983147 A PL 327731 A SK 92598 A ZA 9700171 A		00/00/00 01/08/97 02/10/96 30/04/99 06/04/99 17/07/97 31/03/99 17/02/99 07/01/98 25/11/98 00/00/00 28/07/99 00/00/00 17/11/98 07/11/97 08/09/98 21/12/98 11/01/99 24/07/98

INTERNATIONAL SEARCH REPORT

Information on patent family members			International application No.	
			02/12/99	PCT/DK 00/00190
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 9731907 A1	04/09/97	AP 9700935 D AU 2093597 A BG 102792 A CA 2247443 A CN 1218460 A CZ 9802750 A EP 0888317 A GB 9604242 D HR 970110 A IL 125796 D NO 983940 A PL 328871 A SK 116398 A	00/00/00 16/09/97 31/08/99 04/09/97 02/06/99 13/01/99 07/01/99 00/00/00 30/04/98 00/00/00 27/10/98 01/03/99 13/04/99	
